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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,407	03/14/2001	Takuro Tamura	033808/027 8720	3695

7590 02/10/2005

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,407	TAMURA ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/18/2004 has been entered. Claims 1-5 and 8 have been amended. Claim 9 has been added. Claims 1-9 are pending.

Previous Objections and Rejections

2. The objection to the specification for lack of a proper sequence identifier (SEQ ID NO:) is maintained. The claim rejection under 35 USC 112 second paragraph as being indefinite for the recitation of "visually-intuitive graphical representation" is withdrawn in view of Applicant's amendment. The claim rejection under 35 USC 102(b) directed to claim 1 as being anticipated by Lockhart et al is withdrawn in view of Applicant's amendment to the claims. The prior art rejection under 35 USC 103(a) directed to claims 2-7 as being unpatentable over Lockhart et al in view of Pal is withdrawn in view of Applicant's amendment of the claims. The prior art rejection under 35 USC 102(b) directed to claims 1-6 and 8 as being anticipated by Eisen et al is maintained and discussed below. The prior art rejection under 35 USC 103(a) as being unpatentable over Eisen et al in view of Lockhart is maintained and discussed below.

Objection

3. Once again, the specification is objected to because the specification and drawing contain sequences that are not represented by a proper sequence identifier (SEQ ID NO:) as indicated by the raw sequence listing and CFR (see MPEP§ 2422.03). Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. Once again, claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Eisen et al (PNAS, Vol. 95, pages 14863-14868, December 1998). Regarding claim 1, Eisen et al teach a method of displaying results which a plurality of probe biopolymers are immobilized on a microarray are hybridized to a sample biopolymer, the method comprising determining information obtained in the hybridization experiment about a hybridization level for each of the probe biopolymers; determining probe similarity score representing a similarity between first probe data on a base sequence of at least one of the probe biopolymers and a second probe data on a base sequence of at least one other probe biopolymer; and displaying said information about the hybridization level for each of the probe biopolymers together with said probe similarity score, including generating a visual graphical representation of the determined hybridization level and correspondingly determined probe similarity score that may be intuitive to the biologist so as to provide at least one confirmation of similarities between the base sequences of corresponding biopolymers used in the hybridization experiments and a visual indication of any unexpected hybridization or any other functional information not currently available (see abstract and page 14863 last paragraph of col. 1 to col. 2, lines 1-8, 28-43 and page 14864, entire section entitled "Materials and Methods".

Regarding claim 2, Eisen et al teach the method of claim 1 for display results of a hybridization experiment, wherein said step of generating the visually-intuitive graphical representation include assigning different depths in a color to different values of the probe similarity (page 14864, sections entitled "Metrics", "Hierarchical Clustering" and "Display").

Regarding claim 3, Eisen et al teach the method of claim 1 for displaying results of a hybridization experiment, wherein said step of generating the visually-intuitive graphical representation include assigning different depths in a color to different values of the probe similarity score, and arranging subject probe biopolymer horizontally and vertically to form a matrix (page 14864, sections entitled "Metrics", "Hierarchical Clustering" and "Display").

Regarding claim 4, Eisen et al teach the method according to any one of claims 1-3 for displaying hybridization results, wherein said step of generating the visually-intuitive graphical representation includes displaying the information about the hybridization level by assigning different depths in color to different values of the hybridization level (page 14864, sections entitled "Metrics", "Hierarchical Clustering" and "Display").

Regarding claims 5, Eisen et al teach the method according to any one of claims 1-3 for displaying hybridization results, wherein probe biopolymer data, hybridization levels and probe similarity scores are displayed sided by side by sorting then by values of the probe similarity score between specific one of the probe biopolymers and each of the probe biopolymers. Likewise, Eisen et al teach wherein a profile of changes in the hybridization level of the subject biopolymers on the (page 14864, sections entitled "Metrics", "Hierarchical Clustering" and "Display"; section entitled "Redundant Representations of Gene Cluster Together" and Figures 1 and 2).

Regarding claims 6, Eisen et al teach the method according to claims 5 for displaying results of hybridization experiments, wherein the hybridization levels or hybridization profiles are analyzed on a plurality of different microarrays (biochips) and wherein the hybridization profiles are displayed side by side (page 14867, Figure 3).

Regarding claim 8, Eisen et al teach the method according to claim 1 for displaying results of a hybridization experiment according to claim 1, wherein the probe data on the base sequence of the probe biopolymers for determining the probe similarity score includes at least one of DNA probes names and DNA probe definition information (see Figure 2). Therefore, Eisen et al teach the limitations of claims 1-6 and 8 of the instant invention.

Claim Rejections - 35 USC § 103

5. Once again, claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eisen et al as applied to claims 1-6 and 8 above, and further in view of Lockhart et al (Nature Biotechnology, vol. 14, pages 1675-1680, December 1996). Regarding claim 7, Eisen et al teach a method according claim 6 for displaying results of a hybridization experiment, wherein the hybridization levels obtained from a plurality of microarray are displayed side by side (see figure 3). Eisen et al differs from the instant invention in that the reference does not teach wherein a profile of changes in the hybridization level of the subject biopolymer on the plurality of biochips is statistically analyzed and the results of the analysis are displayed together with the results of clustering the probe biopolymer.

Lockhart teach a method similar to that of Lockhart for displaying the results of a hybridization experiment, the method comprising the step of displaying information obtained in hybridization experiments about a hybridization level for each probe (see whole document

teaching arrays with measuring level of hybridization signal (see figure 3 and 5 and their teaching of phycoerythrin and fluorescein emission in experimental protocol). Lockhart et al teach that the array contains over 65,000 different oligonucleotide probes (see page 1678). Lockhart et al teach wherein a profile of changes in a hybridization level of a subject biopolymer(s) is statistically analyzed (quantitated) and the results of the analysis displayed along with clustering information of the probe biopolymers (see Figures 3-4 for statistical analysis and Figures 2 and 5 for clustering data). Lockhart et al teach that statistical analysis of expression level along with clustering information (quantitative monitoring) proves valuable in elucidating gene function, exploring the causes and mechanisms of diseases and for the discovery of potential therapeutics and diagnostic targets (page 1679, col. 1, second full paragraph). Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the display method of Eisen et al to further encompass results from a statistical analysis as taught by Lockhart et al for the benefits of providing additionally information which may be valuable in elucidating gene function, exploring the causes and mechanisms of diseases and for the discovery of potential therapeutics and diagnostic targets as suggested by Lockhart et al. Likewise, it would have been *prima facie* obvious to apply Lockhart's method of statistical analysis with Eisen's method of displaying clustering of probe biopolymers in order to further enhance visually distinguishing sequence similarities and hybridization intensities.

Applicant's Traversal

6. Applicant traverses the rejection on the following grounds: Applicant summarizes the Examiner's rejections and states that the present invention as now claimed is directed to methods

for displaying results of a hybridization experiments in which a plurality of probe biopolymers immobilized on a biochip are hybridized to a sample biopolymer. Applicant states that the method incorporates the steps of determining information obtained in the hybridization experiment about a hybridization level for each of the probe biopolymer; determining a probe homologous similarity score which represents a homologous similarity between first probe data on a base sequence of at least one probe biopolymer and a second probe data on a base sequence of at least one other of the probe biopolymers and second probe data on a base sequence of at least one other probe biopolymers, according to an algorithm for calculating degrees of homology between two biopolymers (e.g., Smith-Waterman method, BLAST or the like) and displaying the information about the hybridization level for each of the probe biopolymers together with (2) the probe homology similarity score, including generating a visual graphical representation of the determined hybridization level and correspondingly determined probe homologous similarity score so as to provide at lest one of a visual confirmation of similarities between the bases sequences of corresponding biopolymers used in the hybridization experiments and a visual indication of unexpected or improper hybridization. Applicant summarizes examples in the specification and states that Eisen nor Lockhart teaches or suggests at least determining a probe homologous similarity score according to an algorithm for calculating degrees of homology between two biopolymers sequences and then displaying said information about the hybridization level for each of the probe biopolymers together with said probe homologous similarity score so as to provide a visual indication of unexpected or improper hybridization according to the invention. Applicant contends that in contrast, Eisen yeast expression analysis merely clusters probes so as to display a cluster tree diagram and indicates a

hybridization between a probe A and a sample B, but not calculated according to an algorithm for calculating degree of homology between two biopolymer sequences to obtain probe homologous similarity scores which reflect homologous similarity between any two probes. Applicant states that Eisen simply does not provide a visual indication of unexpected or improper hybridization. Applicant states that the invention is specifically directed to displaying the probe homologous similarity score along with the hybridization level data are displayed side-b7-side so to be compared with each other in a manner that is visually easy to understand. Applicant states that the probe homologous similarity score is represented by square patterns having varying color depths (rather than any cluster tree), so as to make the displayed image and consequently the information being represented, more visually intuitive. Applicant states that the secondary references of Lockhart nor pal teaches or suggest generating a visually-intuitive graphical representation of the determined hybridization level and correspondingly determined probe homologous similarity score to show unexpected or improper hybridization. Applicant states that the combination of these reference would fall short of embodying a method having every feature of the present invention as claimed, most especially the features as noted above. Applicant states that since the claims 2-7 recite features in addition to those in independent claim 1 that are already not shown by the cited prior art, these same references cannot be used to render obvious the more specific features of dependent claims 2-7. Applicant asserts that rather the present invention as a whole is distinguishable and thereby allowably over the prior art. Applicant states that although the invention applies general homology analysis between probes rather than between a probe and a sample and then displays the "probe homologous similarity score" along with the hybridization levels to achieve unexpected results or properties.

Applicant concludes that present invention as now claimed is distinguishable and thereby allowable over the rejections raised in the Office Action. Applicant request the rejections be withdrawn.

Examiner's Response

7. All of the arguments filed on 11/18/2004 have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant's arguments that Eisen et al do not teach or suggest at least "determining a probe homologous similarity score according to an algorithm for calculating degrees of homology between two biopolymer sequences" and then displaying said "displaying said information about the hybridization level for each of the probe biopolymer together with said probe homologous similarity score..., the Examiner respectfully disagree because the reference of Eisen et al do teach determine a probe homologous similarity score according to an algorithm for calculating degree of homology between two biopolymer sequence and then displaying said information (see specifically page 14864, section entitled "Materials and Methods"). Specifically, Eisen states that at the bottom of column 1 on page 14864 that similarity matrix is computed by using the metric (algorithm) describe above, which contains similarity scores for all pairs of genes. In column 2 at page 14864, Eisen et al teach that the matrix is scanned to identify the highest value (representing the most similar pair of genes). Eisen et al further states that this algorithm can be obtained from the authors at http://rana.stanford.edu/clustering. Furthermore, it appears that Applicant believes the use of the term "homologous" limits the scope of the invention. However, Applicant's specification clearly teaches at pages 3 and 13, that "homology score" or "degree of homology

refers to "similarity score", which is taught by Eisen. Further in regards to displaying said information, Eisen teaches on page 4866 wherein the "similarity scores are displayed "visually" in a graphical representation by changes in color patterns along with probe names and definition information (see Figures, especially Figure 2) as required by Applicant's information. In regards to Applicant's arguments that Eisen doesn't teach the analysis of probe versus probe, it is noted that Eisen et al do teach comparison of probe versus probe as indicated in the Figures, especially figure 2. Likewise at page 14864, Eisen teaches that the similarity matrix is computed by using the metric (algorithm) described above, which contains similarity scores for all pairs of genes, hence probe biopolymer versus probe biopolymer. In response to Applicant's argument concerning the secondary reference of Lockhart, it s noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the primary reference of Eisen teaches determining probe homologous similarity score using an algorithm for calculating degree of homology and displaying same information along with hybridization intensities. The reference does not teach wherein a profile of changes in the hybridization levels is statistically analyzed as required in the claim 7. The secondary reference of Lockhart provides the limitations not found in Eisen. Lockhart teaches a method of a method of comparing similarities between probes on a biochip and displaying results of hybridization experiments for each probe. While Lockhart does not provide an algorithm for calculating the similarities between the probes, Lockhart discloses profiles of changes in the hybridization levels of probe biopolymers and provides statistical analysis of results obtained therein. Lockhart further teaches displaying theses results in a visual

graphical representation. Lockhart provides motivation for wanting to carry out statistical analysis of the changes in hybridization levels of probe biopolymers in the teaching that statistical analysis of expression level along with clustering information (quantitative monitoring) proves valuable in elucidating gene function, exploring the causes and mechanisms of diseases and for the discovery of potential therapeutic and diagnostic targets. In regards to Applicant's arguments concerning "unexpected results", based on the teaching found in the prior art and the claims as written, no unexpected results can be determined by the Examiner. Applicant's arguments are not sufficient to overcome the prior art rejections. Accordingly, the rejections noted above are maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Lockhart et al (US 6,3443126 B1, effective filing date January 1996). Regarding claims 1 and 9, Lockhart et al teach a method of displaying results which a plurality of probe biopolymers are immobilized on a microarray are hybridized to a sample biopolymer, the method comprising determining information obtained in the hybridization experiment about a hybridization level for each of the probe biopolymers; determining probe homologous similarity score representing a homologous

similarity between first probe data on a base sequence of at least one of the probe biopolymers and a second probe data on a base sequence of at least one other probe biopolymer, according to an algorithm for calculating degrees of homology between two biopolymer sequences, wherein said algorithm is a Smith-Waterman method; a FASTA method or BLAST method or the like (col. 9, line 49 to col. 10, line 15 and col. 39, lines 4-38); and displaying said information about the hybridization level for each of the probe biopolymers together with said probe homologous similarity score, including generating a visual graphical representation of the determined hybridization level and correspondingly determined probe similarity score that may be intuitive to the biologist so as to provide at least one confirmation of similarities between the base sequences of corresponding biopolymers used in the hybridization experiments and a visual indication of any unexpected hybridization or any other functional information not currently available (see col. 3, lines 15-65; col. 4, lines 11-24; col. 10, lines 33 to col. 11, lines 53 along with Figures 2-6,15e, 16-17, 24- 27, 31 and 32. See also col. 17-19 and col. 37, section entitled "Heuristic Rules). Therefore, Lockhart et meet the limitations of claims 1 and 9 of the instant invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 2-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al as previously applied above for claims 1 and 9, in view of Tatusova et al (FEMS Microbiology Letters, 175, pages 247-250, 1999 in view of Pal et al (6,528,264). The teachings of Lockhart et al are described previously. Regarding claims 2-8, Lockhart et al do not teach color assignment in display or multiple chips. Likewise, Lockhart et al do not teach wherein the probe homologous similarity score performed by the algorithms includes at least one of DNA probes names, DNA probe definition and DNA probe sequences.

Tatusova et al teach a method similar to that of Lockhart et al for comparing multiple nucleotide sequences using a standard BLAST program. The program provides a graphical representation of the sequences in a dot blot picture and provides statistic information, probe sequence and definition information (see entire reference, pages 247 -250). Tatusova et al do not teach color assignments in the dot blot picture display or multiple chips.

Pal et al teach displaying intensity of signals with color differentiation and comparing different biochips (see Figures 3A-D & col. 6, lines 24-36 and Figures 6A-6D). In view of the foregoing, one of ordinary skill in the art would have been motivated to apply Pal et al's multiple chips and color display to Lockhart et al's microarray and Tatusova et al's dot blot picture in order to visualize differences of hybridization against a plurality of different samples. It would

have been *prima facie* obvious to apply Pal's et al multiple chips and color display to Lockhart et al's and Tatusova et al's method of analyzing multiple nucleic acids samples simultaneously with facility of visually distinguishing the sequence similarity as suggested by Pal et al.

Conclusion

12. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

CYNTHIA WILDER
PATENT EXAMINER
2/4/2005